REMARKS

Entry of this response and reconsideration of the above-referenced application is respectfully requested. Reconsideration and withdrawal of the rejections set forth in the Office Action dated January 17, 2007 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this response.

I. Rejections under 35 U.S.C. §103

Claims 1, 4-7 and 14-24 were rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Manz *et al*. (U.S. Patent No. 6,280,589) in view of Krivankova *et al*. (*J. Chromatography B*, **689**:13-34, 1997).

Claims 1, 4-7, and 14-24 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shultz-Lockyear *et al.* in view of Krivankova *et al.*

Dependent claims 11-12 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Manz *et al*. in view of Krivankova *et al*., as applied to parent claim 1 above, and further in view of Ramsey (U.S. Patent No. 6,342,142).

Claims 11-12 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shultz-Lockyear *et al*. in view of Krivankova *et al*., and further in view of Ramsey.

Claim 13 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Manz *et al*. and Krivankova *et al*. in view of Fuchs *et al*. (U.S. Patent No. 5,630,924). Claim 13 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shultz-Lockyear *et al*. and Krivankova *et al*. in view of Fuchs *et al*.

Claims 1 and 13 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Fuchs *et al.* in view of Krivankova *et al*. and either Manz *et al.* or Shultz-Lockyear *et al.*

These rejections are respectfully traversed in light of the following remarks.

A. The Present Claims

Independent claim 1 is directed to a method of electrophoretically injecting a sample containing multiple charged components into a microfluidic device and

electrophoretically separating the components. The method as claimed employs a two-electrode injection step and a two-electrode separation step, and combines this voltage control scheme with ITP stacking in the same channel. This method produces detectable peaks of high sharpness and resolution, while maintaining high sample volume, thus producing high peak intensities as well.

B. The Cited Art

Manz et al. describes, in the Background section and at column 5, lines 31-58, a two-electrode sample injection process, in which sample is introduced into a main channel by applying an appropriate voltage to each of two channels intersecting the main channel, one of which contains sample. A problem with this process, as described by Manz *et al.* (e.g. at column 1, lines 51-67 and column 5, lines 59-63), is leakage of residual sample from the side channel(s) into the main channel after sample introduction is formally completed.

Krivankova et al. describes the phenomenon of "sample induced stacking" or "sample induced transient ITP". It illustrates a coupled system where transition occurs from an ITP stacking mode to a CZE mode. The systems described employ capillaries, not microfluidic channels.

SHULTZ-LOCKYEAR ET AL. relate to the effects of injector geometry and sample matrix on sample loading of an electrophoretic device.

RAMSEY relates to a microchip apparatus and method for fluidic manipulations.

FUCHS ET AL. is directed to an assay method in which an analyte binds with a first binding partner, which is labeled, and with a second binding partner, which is modified to impart a significant charge. The binding partners are typically modified antibodies. The method is stated to improve over previous assays which did not employ the second binding partner, and where electrophoretic separation of unbound analyte from bound complex was less effective. (See, for example, column 1, lines 45-59 and column 2, lines 44-58.)

While there is a general description of electrophoretic mobility of species in Fuchs (column 16, lines 15-52), there is no description of particular voltage-controlled

injection schemes, and, in fact, injection may be carried out using a pump rather than by voltage control (column 21, lines 26-38).

One stage of the assay in Fuchs involves mixing of the analyte and binding partners. One way of mixing these components is noted at column 23, lines 51-53, where "the elements of the mixture were concentrated in an electric field using a technique such as isoelectric focusing or isotachophoresis". There is no other reference to isotachophoresis (ITP) in the patent.

C. Analysis

1. Rejection over Manz *et al.* in view of Krivankova *et al.*

The combination of Manz *et al.* and Krivankova *et al.* fails to teach a method as presently claimed. Manz *et al.* teach a capillary electrophoresis method and device here a sample is injected as a sample plug into a device which comprises at least an electrolyte channel and supply and drain channels. As noted by the Examiner, "Manz *et al.* do not explicitly disclose a method in which the sample solution and background electrolyte are chosen such that the first and second electrolyte solutions each comprise an ion having lower mobility in an electric field than any of said charged components, and one or the other of said electrolyte solutions comprises an ion having higher mobility in an electric field than any of said charged components" (Office action mailed January 17, 2007, pages 4-5) as in isotachophoresis stacking. The Examiner relies upon Krivankova *et al.* for teaching a method of sample stacking in capillary electrophoresis. However, a careful reading of Krivankova *et al.* would not lead one skilled in the art to perform both ITP and CZE as in the present method. The Examiner is respectfully directed to page 18, col. 2, last paragraph of Krivankova, which states "The capillary used for the ITP step must provide sufficient separation capacity and reproducible sampling of a relatively large volume of a sample. Therefore a capillary of wider diameter equipped with a sample valve is recommended for this step. A capillary of a narrower diameter equipped with a sensitive detector is used in the CZE step and it ensures sensitivity of analysis." Further, Figure 9 on page 22 shows the ITP performed

in a wider capillary than the CZE. It is further noted that Figure 9 shows the leading electrolyte is not transferred to the CZE capillary.

A person of skill confronted with the problem faced by the present inventors, would not select from Krivankova *et al.* the sole feature of ITP without taking into account the entire teaching of Krivankova *et al.* Rather, the solution to this problem according to the teaching of Krivankova *et al.* is to employ separate capillaries for ITP and CZE. The Examiner has conveniently selected from Krivankova *et al.* a particular feature simply in order to recreate the presently claimed method.

2. Rejection over Shultz-Lockyear *et al.* in view of Krivankova *et al.*

One skilled in the art would not be motivated to combine the cited references along the lines of the present method as the two references describe systems having significant structural differences and uses, and are directed to different perceived problems and benefits. Similar to the Manz *et al.* reference, Shultz-Lockyear *et al.* describes a system in which sample is electrokinetically introduced into a main separation channel region between side channels in a "double T" configuration. Injection of the sample plug into the electrolyte channel is accomplished electro-kinetically by applying an electric field across the supply and drain channels. Krivankova *et al.*, on the other hand, describe the usefulness of preceding capillary zone electrophoresis (CZE) with a preconcentration step employing capillary isotachophoresis (ITP) where the ITP and CZE are performed in different sized capillaries.

3. Rejection over Manz *et al.* and Krivankova, and further in view of Ramsey

Dependent claims 11-12 are directed to types of analytes that may be used in the method of claim 1.

The deficiencies in the combination of Manz *et al.* in view of Krivankova *et al.* are detailed above. With respect to the subject matter of independent claim 1, Ramsey *et al.* do not make up for the deficiencies of this combination of references as Ramsey *et al.* make no mention of ITP or combining ITP and CZE.

Accordingly, claim 1 and its dependent claims are nonobvious over this

combination of references.

4. Rejection over Shultz-Lockyear *et al.* and Krivankova *et al.*, and further in view of Ramsey

For the reasons discussed above, Shultz-Lockyear *et al*. in view of Krivankova *et al*. does not teach or suggest the method of claim 1. With respect to the subject matter of independent claim 1, Ramsey *et al*. does not make up for the deficiencies of this combination of references as Ramsey *et al.* make no mention of ITP or combining ITP and CZE.

5. Rejection over Manz *et al.* and Krivankova, and further in view of Fuchs *et al.*

The deficiencies in the combination of Manz *et al*. in view of Krivankova *et al*. are detailed above. Nor does Fuchs *et al.* make up for these deficiencies. Fuchs *et al*. does not suggest the advantages of ITP in a separation method. As stated above, the only reference to ITP in Fuchs is as one way of mixing the assay components: "the elements of the mixture were concentrated in an electric field using a technique such as isoelectric focusing or isotachophoresis". Presumably, the assay components are "concentrated" to facilitate reaction (binding) before the separation and detection of bound complex is carried out.

6. Rejection over Shultz-Lockyear *et al.* and Krivankova *et al.*, and further in view of Fuchs *et al.*

As described above, the combination of Shultz-Lockyear *et al*. in view of Krivankova *et al*. does not teach or suggest the present method. Nor does Fuchs *et al.* make up for the deficiencies of this combination of references. As noted above, Fuchs *et al*. does not suggest the advantages of ITP in a separation method.

7. Rejection over Fuchs *et al.* in view of Krivankova *et al.* and either Manz *et al.* or Shultz-Lockyear

The deficiencies of the combination of Fuchs *et al.* with Krivankova *et al.*, and either of Manz *et al.* or Shultz-Lockyear *et al.* is addressed above. Briefly, the combinations of references fail to show or suggest motivation to combine the references along the lines of the present method.

In view of the foregoing, Applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

II. Conclusion

In view of the foregoing, Applicants submit that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

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